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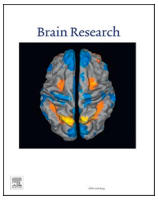

Review

Was it something I ate? Understanding the bidirectional interaction of migraine and appetite neural circuits

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ABSTRACT

Migraine attacks can involve changes of appetite: while fasting or skipping meals are often reported triggers in susceptible individuals, hunger or food craving are reported in the premonitory phase. Over the last decade, there has been a growing interest and recognition of the importance of studying these overlapping fields of neuroscience, which has led to novel findings. The data suggest additional studies are needed to unravel key neurobiological mechanisms underlying the bidirectional interaction between migraine and appetite. Herein, we review information about the metabolic migraine phenotype and explore migraine therapeutic targets that have a strong input on appetite neuronal circuits, including the calcitonin gene-related peptide (CGRP), the pituitary adenylate cyclase-activating polypeptide (PACAP) and the orexins. Furthermore, we focus on potential therapeutic peptide targets that are involved in regulation of feeding and play a role in migraine pathophysiology, such as neuropeptide Y, insulin, glucagon and leptin. We then examine the orexigenic - anorexigenic circuit feedback loop and explore glucose metabolism disturbances. Additionally, it is proposed a different perspective on the most reported feeding-related trigger - skipping meals - as well as a link between contrasting feeding behaviors (skipping meals vs food craving). Our review aims to increase awareness of migraine through the lens of appetite neurobiology in order to improve our understanding of the earlier phase of migraine, encourage better studies and cross-disciplinary collaborations, and provide novel migraine-specific therapeutic opportunities.

1. Introduction

Diet has been implicated in migraine over decades (Dalton, 1975; Dalton, 1977; Dalton and Dalton, 1979; Diamond et al., 1986; Medina and Diamond, 1978). In the clinical setting dietary guidelines rely on elimination of extensive lists of food triggers to prevent migraine attacks in headache patients (Mahan and Raymond, 2017), offering neither a strong rationale nor objective data to support the advice. These triggers are primarily based on retrospective reports from patients and can include a diverse list of foods including chocolate, dairy products, eggs,

Abbreviations: **AgRP**, Agouti-related peptide; **ARC**, Arcuate nucleus of the hypothalamus; **BMI**, Body mass index; **CART**, Cocaine-and amphetamine-regulated transcript; **CGRP**, Calcitonin gene related peptide; **CGRP^{PBN}**, CGRP neurons in the PBN; **CNS**, Central nervous system; **DMH**, Dorsomedial nucleus of the hypothalamus; **GI**, Gastrointestinal; **GTN**, Glyceryl trinitrate; **HGP**, Hepatic glucose production; **i.c.v**, intracerebroventricular; **LC**, Locus coeruleus; **LH**, Lateral hypothalamus; **MMA**, Middle meningeal artery; **MCH**, Melanin-concentrating hormone; **Nac**, Nucleus accumbens; **NPY**, Neuropeptide Y; **NTS**, Nucleus tractus solitaries; **ObRb**, Leptin receptor b; **PACAP**, Pituitary adenylate cyclase activating polypeptide; **PAG**, Periaqueductal gray; **PeF**, Perifornical area of the hypothalamus; **PFC**, Prefrontal cortex; **POMC**, Proopiomelanocortin; **PBN**, Parabrachial nucleus; **PVN**, Paraventricular nucleus of the hypothalamus; **SCN**, Suprachiasmatic nucleus; **Sp5c**, Spinal trigeminal nucleus caudalis; **SSS**, Superior sagittal sinus; **TCC**, Trigeminocervical complex; **VMH**, Ventromedial nucleus of the hypothalamus; **VTA**, Ventral tegmental area.

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citrus fruits, artificial sweeteners, sweetened beverages, alcoholic beverages, etc. (Fukui et al., 2008; Millichap and Yee, 2003). The fact that these foods/drinks have very little in common, often lead to no useful outcome, and with emerging clinical (Giffin et al., 2003b; Karsan et al., 2020b; Onderwater et al., 2020) and imaging data (Karsan and Goadsby, 2020; Maniyar et al., 2013) on the premonitory phase of migraine, led us to question whether appetite pathways overlap with migraine pathophysiology (Goadsby et al., 2017; Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a; Martins-Oliveira et al., 2017b) to create the illusion of a trigger. Currently, investigation of the premonitory phase of the migraine has expanded, with several neuroimaging studies in induced- and spontaneous- migraine attacks in headache patients (Maniyar et al., 2013; Schulte et al., 2015; Sprenger and Goadsby, 2010). However, many questions remain to formulate a better understanding of appetite neurobiology in migraine.

To address gaps in understanding in these overlapping fields of neuroscience, this review presents the metabolic migraine phenotype, introduces key appetite-regulating peptides with a role in migraine pathophysiology, and analyzes different perspectives on feeding-related triggers. This narrative review is a non-systematic summation and analysis of available literature, with no formal guidelines. We divided the literature into several sections/themes, compare and contrast ideas and findings of multiple sources, and then interpret and critically evaluate it to make an overall point throughout each section of the manuscript. We recapitulate important features of historical studies in both fields and aim to synthesize it by rephrasing the study's significance relating it to our topic. Overall, the review blends independent, and apparently unrelated, ideas and findings into an original and novel perspective of the intersection of appetite and migraine.

2. Appetite changes, gastrointestinal (GI) function and the metabolic phenotype in migraine

Migraine is an inherited, episodic disorder involving sensory sensitivity (Goadsby and Holland, 2019), whose key marker is headache, with certain associated features, such as nausea, photophobia and phonophobia (Headache Classification Committee of the International Headache Society (IHS), 1988), and, in one-fifth of patients, an aura with neurologic symptoms (Lance and Goadsby, 2005). It has been classically dissected into four phases that may occur in a linear sequential order, although in most cases show a significant overlap: the premonitory, aura, headache and the postdrome phase (Akerman et al., 2011; Goadsby et al., 2002). Premonitory symptoms can include thirst and changes in appetite (hunger and/or food craving), as well as mood changes, tiredness or yawning, indicating an underlying hypothalamic dysfunction (Giffin et al., 2003b). Importantly, premonitory symptoms are more common than aura symptoms (Karsan and Goadsby, 2018), which suggests their understanding is important.

Migraineurs experience attacks and report they are preceded by triggering factors, such as food deprivation or fasting/skipping meals (Dalkara and Kiliç, 2013). In one study, Martin and Seneviratne (Martin and Seneviratne, 1997) found that food deprivation was associated with headache in 58% of patients with frequent migraine or tension-type headache. Moreover, Blau and Cumings (Blau and Cumings, 1966) reported that fasting caused headache in 50% of migraineurs and concluded "some patients have some of their attacks of migraine fired off by missing a meal, and that this is related to a low blood sugar, which must persist in that individual for a certain length of time to cause headache". Conversely, there are many observations of food cravings during the premonitory phase of migraine, with researchers reporting that some patients would crave for sweet or highly palatable foods, for example chocolate (Drummond and Lance, 1984a). Studies revealed that around 18% of the patients report food cravings or hunger as triggers of their headache (Giffin et al., 2003a; Schoonman et al., 2006), with no significant differences between migraine with or without aura (Schulte et al., 2015).

It is still debated whether some foods, which incidentally are highly palatable, are actually triggers or rather that food craving is a symptom in the premonitory phase of migraine. Some authors attempted to reconcile these factors - food deprivation, hunger and food cravings, suggesting that "hunger arising from low blood sugar levels, for example, may lead to cravings for particular foods such as chocolate, on the one hand, and lead to headaches, on the other hand, but the headaches may be erroneously attributed to the food consumption rather than the low blood sugar levels" (Martin and Seneviratne, 1997). Nevertheless, studies fail to discriminate if susceptible migraineurs specifically reporting premonitory food cravings experienced food deprivation or skipped meal hours before food craving. Remarkably, in patients who report they have food triggers, 81% report hunger or cravings during the premonitory phase of a nitroglycerin-induced attack (Karsan et al., 2020b).

Regarding body weight, studies report weight change is a side-effect commonly associated with medications used for migraine prophylaxis, although studies do not report appetite changes (Taylor, 2008; Young, 2008). It is suggested these medications impact appetite and feeding behavior probably through hypothalamic pathways, for instance leptin resistance (Berilgen et al., 2005). The exact mechanism is currently unknown, and it is also possible these medications interfere with basal metabolic rate, which is another physiological way of impacting body weight. Prophylactic treatment is therefore a factor that should be considered when interpreting these studies.

The biopsychosocial model of feeding behavior is also relevant in migraine pathophysiology. On one hand, patients with migraine are at increased risk for major depression and anxiety when compared to subjects without migraine (Dresler et al., 2019), which are known to cause appetite changes. On the other hand, some premonitory symptoms related to sensory processing may also impact feeding behavior, for instance osmophobia. Appetite regulation involves integration of gastrointestinal physiology, neurobiology as well as cognitive and behavioral sciences. The sense of smell plays a role in the homeostatic and hedonic aspects of feeding and contributes to building and maintaining well-being through supporting nutrition and social relationships, yet scientific evidence is scarce to confirm it affects actual food ingestion and underlying mechanisms (Boesveldt and Parma, 2021; Fine and Riera, 2019). What is understood is disturbances of olfaction can lead to weight loss driven by psychological factors (e.g. depression) (Fine and Riera, 2019). Although there is no human data correlating osmophobia and appetite changes in the premonitory phase of the migraine attack, it is possible that patients feel less inclined to eat certain foods during this phase.

Migraine has been associated with gastrointestinal (GI) dysfunction. For instance, GI complaints increase with increasing headache frequency, migraines are often accompanied by various GI symptoms, and patients with migraine are more prone to GI disorders (Aamodt et al., 2008; Lee et al., 2017). Given this association, it has been suggested the gut microbiota might play a pivotal role in migraine through the gut–brain axis (Gazerani, 2021). In addition, animal studies have shown that appetite-regulating hormones are under the influence of the gut microbiota (Holzer, 2016), though a causal association in migraine patients is lacking. Diet is perhaps one of the greatest factors influencing microbiota composition and many conditions wherein food intake behavior is dysregulated are associated with an altered gut microbiota, that might affect the ability to sense and taste nutrients (Cryan et al., 2019). Interventions with probiotics help improve gut microbiota and several probiotic trials in migraine patients have been published (Arzani et al., 2020). Nonetheless, a systematic review (Naghibi et al., 2019) concluded that there is a clear lack of consistency in the results and a recent meta-analysis (Parohan et al., 2020) confirmed probiotic supplementation had no significant effect on the frequency and severity of episodic migraine attacks.

Furthermore, a correlation between migraine and abnormal glucose metabolism has been suggested and clinical studies have shown some

evidence of an altered insulin and glucose metabolism in migraineurs. Two clinical studies consistently show higher insulin levels in migraineurs than in controls (Cavestro et al., 2007; Rainero et al., 2005) implying that insulin resistance is present in migraineurs. Interestingly, Critchley and Ferguson (Critchley and Ferguson, 1933) stated that "migraine attacks induced by hunger or fasting were unlikely to be directly related to absolute blood glucose levels and nor does it seem likely that such attacks were related to the rapidity of the fall in venous blood sugar". Perhaps what these studies demonstrate most is a likely adaptive response to the shift of glucose metabolism in migraine patients (this will be further discussed in 5. Glucose metabolism disturbances in migraine: the role of appetite-regulating peptides and 6. Fasting and/or skipping meals in migraine: voluntary or loss of appetite?).

3. Appetite-regulating peptides and relevance to migraine pathophysiology

Migraine pathophysiology is thought to involve activation and sensitization of trigeminovascular nociceptive pathways that innervate the cranial vasculature, and activation of brainstem nuclei (Akerman et al., 2013). The trigeminovascular system relevant to headache includes the pseudo-unipolar trigeminal ganglion neurons and their projections to the trigeminal nucleus caudalis (TNC) and C1 and C2 regions in the medullary and cervical spinal cord – the trigeminocervical complex (TCC), and its peripheral afferent projections mainly from the ophthalmic division (V1) of the trigeminal nerve to the cranial blood vessels and other cranial structures, including the dura mater (Akerman et al., 2011). Stimulation of the dural vasculature produces neuronal activation in the TNC, and is likely painful in humans (Feindel et al., 1960; Penfield and McNaughton, 1940) because the vascular structures of the dura mater, including the superior sagittal sinus (SSS) and middle meningeal artery (MMA), are richly innervated by a plexus of largely unmyelinated sensory nerve fibers from the ophthalmic division of the trigeminal ganglion (Akerman et al., 2013). Preclinical models have taken advantage of this primarily nociceptive pathway, the dural trigeminovascular nociception, to examine aspects of head pain thought to be involved in migraine (Bergerot et al., 2006; Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a).

Regarding appetite, metabolism and feeding behavior, several brain structures are involved as a synchronized network (Palmiter, 2018; Sohn et al., 2013; Yeo and Heisler, 2012). The hypothalamus is a major center of convergence and integration of several nutrient-related signals (an integrated view is presented in Fig. 1) and, thus, hypothalamic neurons are thought to promote the homeostasis of physiological systems involved in synchronization of circadian rhythms, salt balance, appetite and energy expenditure, thirst and water balance, among other functions (Rolls et al., 2010). Neuroimaging studies in the premonitory phase have demonstrated activation of the hypothalamus and a region consistent with the ventral tegmental area (VTA) (Maniyar et al., 2014), while a somewhat different hypothalamic site is activated during the attack (Denuelle et al., 2007). This is in agreement with earlier animal studies (Bartsch et al., 2004b; Benjamin et al., 2004a; Burstein et al., 1987; Malick et al., 2000), establishing the hypothalamus as an important brain area in migraine pathophysiology (Charbit et al., 2009) (Benjamin et al., 2004b; Malick and Burstein, 1998). For instance, stimulation of the dura mater in the rat produces Fos expression in the ventromedial (VMH), paraventricular (PVN) and dorsomedial hypothalamic nuclei (DMH), resulting in suppression of appetite and in increases in arterial blood pressure (Malick et al., 2001); and stimulation of the SSS in the cat results in hypothalamic activation with up-regulation of Fos protein-like immunoreactivity in the supra-optic and posterior hypothalamic nucleus (Benjamin et al., 2004b). Therefore, experimental data suggest that hypothalamic structures can directly regulate trigeminovascular nociceptive afferent traffic. In addition, the hypothalamus is in a strategic position to receive neuronal inputs from other appetite-regulating structures to impact on some of the

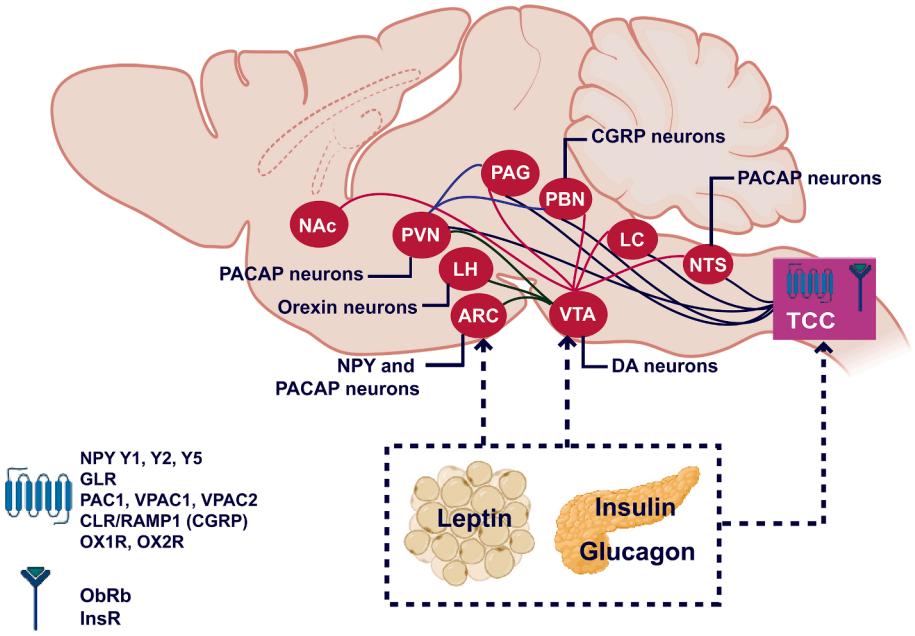

Fig. 1. Feeding neuronal circuits that interact with the trigeminocervical complex (TCC) and other brain stem nuclei involved in pain modulation. Peripheral circulating hormones produced by the adipose tissue and pancreas interact with hypothalamic arcuate (ARC) neurons containing neuropeptide Y (NPY)/ agouti-related peptide and proopiomelanocortin /cocaine and amphetamine- regulated transcript to regulate food intake and energy expenditure. These circulating hormones also influence the midbrain ventral tegmental area (VTA) and the TCC in the medulla. The circuitry of energy homeostasis comprises ARC neurons that transmit information to specific nuclei within the hypothalamus, including the paraventricular nucleus (PVN) and the lateral hypothalamus (LH). The ventral tegmental area (VTA) receives information from ARC neurons and comprises the dopaminergic mesolimbic pathway (nucleus accumbens (NAc)) involved in processing hedonic feeding, i.e., motivation to ingest highly palatable food. These nuclei may play a putative role in migraine pathophysiology through their descending projections to brain stem nuclei known to be involved in the modulation of headache-related pain processing. These include PVN direct projections to the TCC and indirect projections to the periaqueductal grey (PAG) and parabrachial nucleus (PBN). Moreover, indirect communication through VTA projections to the PAG, PBN, the locus coeruleus (LC), and the nucleus tractus solitarius (NTS) might also modulate TCC nociceptive activity. Of note, the TCC contains transmembrane receptors for leptin (ObRb) and insulin (InsR), as well as G-protein couple receptors for NPY (NPY Y_1, Y_2, Y_5), glucagon (GLR), PACAP (PAC_1, $VPAC_1$ and $VPAC_2$), CGRP (heterodimer composed of CLR, calcitonin-like receptor/ RAMP1, receptor activity-modifying protein) and orexins (OX1R, OX2R). Given that altered feeding affects neuronal processing in these appetite-regulating structures, it is likely that their physiological control of transmission of nociceptive inputs to the trigeminovascular system will be disturbed. This could lead to abnormal activation of the trigeminovascular system and altered perception of craniofacial pain.

premonitory symptoms. It is the case of the VTA, a major midbrain structure, we have recently shown is able to modulate trigeminovascular neuronal firing in response to nociceptive vascular electrical and facial mechanical stimulation, impacting glucose metabolism (Martins-Oliveira et al., 2017b). Specific appetite-related peptides that are known to act within the hypothalamus and the VTA will be discussed in detail below.

3.1. Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide produced by alternative splicing of the calcitonin gene (Amara et al., 1982; Rosenfeld et al., 1983). Anatomical studies revealed that CGRP is widely distributed in the CNS including in the hypothalamus, thalamus, striatum, amygdala, brain stem, and the TCC (Hökfelt et al., 1992; van Rossum et al., 1997; Yasui et al., 1991). In addition, CGRP is highly expressed in the sensory trigeminal ganglion, including its fiber projections to cerebral and dural vasculature and to the spinal cord (Edvinsson et al., 1998; Eftekhari et al., 2010; Tajti et al., 1999).

Based on molecular cloning studies, CGRP acts at one receptor clearly: the canonical CGRP-receptor complex, made up of a G protein-coupled receptor consisting of a seven transmembrane spanning protein (calcitonin receptor-like receptor; CLR) and a single transmembrane receptor modifying protein (RAMP) 1 (Aiyar et al., 1996; McLatchie et al., 1998); and may act at another, the non-canonical amylin receptor (AMY_1) that consists of the calcitonin receptor (CTR) and RAMP1 (Hay et al., 2015). Recently, it has been shown that CGRP activates this receptor in the rat and human sensory trigeminal system (Walker et al., 2015). Moreover, functional CGRP receptors have been identified in the trigeminal ganglia, brain stem, hypothalamus, thalamus, amygdala, cerebellum, and cortex (Edvinsson et al., 2011; Eftekhari et al., 2010; Lennerz et al., 2008; Oliver et al., 2002; Summ et al., 2010; Warfvinge and Edvinsson, 2017). Specifically, a study in primates, using antagonist antibodies against CGRP, demonstrated binding to human vascular smooth muscle cells (VSMCs) of dural meningeal arteries and neurons in the trigeminal ganglion, and in monkeys in the dura mater vascular smooth muscle cells, in neurons and satellite glial cells in the trigeminal ganglion, and in neurons in the spinal trigeminal nucleus caudalis (Miller et al., 2016). Interestingly, in the TCC, CGRP receptors seem to colocalize with CGRP in terminals of primary afferents but not ascending fibers (Lennerz et al., 2008).

Moreover, CGRP has potent vasodilator effects (Kurosawa et al., 1995; Williamson et al., 1997) and is known to trigger attacks when given to migraine sufferers (Lassen et al., 2002). Clinical studies have shown that CGRP is released during spontaneous (Goadsby et al., 1990) or triggered attacks (Gallai et al., 1995), which can be inhibited by triptan treatment (Goadsby and Edvinsson, 1993). Regarding non-headache features, RAMP1 is critical for the transport and cell surface expression of the CGRP receptor complex (McLatchie et al., 1998), and its overexpression results in migraine-like phenotypes such as light aversion and allodynia (Kaiser et al., 2012; Recober et al., 2009; Russo et al., 2009). In fact, mice with a gain-of-function mutation of CGRP receptor exhibit light aversion behavior when they receive a CGRP injection (Kaiser et al., 2012). Other animal studies report that local administration of CGRP facilitates TCC nociceptive neurons, while CGRP antagonism inhibited neuronal responses (Storer et al., 2004). In the brain, CGRP delivery into the ventrolateral PAG facilitates trigeminovascular processing via descending modulatory mechanisms (Pozo-Rosich et al., 2015), while CGRP antagonist delivery into the thalamus inhibited both nociceptive signaling and spontaneous background activity (Summ et al., 2010). Consistent with this view, CGRP-induced spontaneous facial grimace pain was completely blocked by pre-administration of a monoclonal anti-CGRP-blocking antibody (Rea et al., 2018).

For decades, endogenous CGRP has been shown to be a key regulator of metabolism and energy homeostasis *in vivo*. In normal weight humans, a high-fat meal caused a sustained increase of plasma CGRP concentrations, whereas no change of CGRP was observed after an isocaloric high-carbohydrate meal (Zelissen et al., 1991). Moreover, plasma CGRP concentration was increased in obese women compared to normal-weight controls and significant weight reduction (but still obese) did not result in a decrease of these levels. (Zelissen et al., 1991). In animals, peripheral and central administration of CGRP acutely decreased food intake (Krahn et al., 1984; Morley et al., 1996; Sun et al., 2010; Tannenbaum and Goltzman, 1985) and peripheral treatment reduced plasmatic glucagon and leptin levels (Sanford et al., 2019).

The CGRP key role in feeding behavior is mediated by the parabrachial nucleus (PBN) (Palmiter, 2018). Using genetically encoded tools, it has been demonstrated that CGRP neurons in the PBN ($CGRP^{PBN}$) control meal termination since functional inactivation of these neurons increases meal size and duration, but has no effect on total food intake over time (Campos et al., 2016). Supporting the overall anorexigenic CGRP role, stimulation of $CGRP^{PBN}$ neurons rapidly and reversibly reduces food intake (Campos et al., 2016; Carter et al., 2013). Furthermore, there is an interaction between the PBN and the hypothalamus that mediates food intake during appetite suppressing conditions. For instance, stimulation of agouti-related peptide (AgRP) neurons ameliorated appetite suppression caused by chemogenetic stimulation of $CGRP^{PBN}$ neurons (Essner et al., 2017). Consistent with these data, noxious dural stimulation in an animal model of intracranial headache-like pain increased Fos-positive neurons in the PBN and the ventromedial hypothalamus (VMH) and induced a transient suppression of food intake (Malick and Burstein, 2001). These observations suggest that it is likely that $CGRP^{PBN}$ neurons mediated this anorexigenic effect.

Furthermore, metabolic experiments suggest that CGRP may impair insulin secretion and action. More precisely, CGRP has been shown to inhibit insulin secretion *in vitro* (Pettersson et al., 1986) and inhibit the ability of insulin to stimulate glucose incorporation into skeletal muscle glycogen at physiological insulin concentrations in an isolated rat soleus muscle preparation (Leighton and Cooper, 1988). In conscious animals, CGRP induces insulin resistance by decreasing glucose uptake and increasing hepatic glucose production (Choi et al., 1991). In hyperinsulinemic glucose-clamp studies in rats infused with both insulin and CGRP, a marked state of *in vivo* insulin resistance was induced and this effect was rapidly reversible on CGRP withdrawal (Molina et al., 1990). Moreover, CGRP regulates core body temperature and energy expenditure, and CGRP knockout mice present better glucose tolerance and insulin sensitivity, than wild-type mice (Liu et al., 2017). Consistent with this view, it is possible that CGRP release contributes to altered glucose metabolism observed in migraine patients (Bernecker et al., 2010; Cavestro et al., 2007; Fava et al., 2013; Rainero et al., 2005; Siva et al., 2017).

While most acute symptomatic treatments for migraine have the potential to worsen migraine with frequent use (Diener et al., 2016), antagonism of the CGRP pathway is effective both acutely and chronically for migraine prevention (Edvinsson et al., 2018). The development of monoclonal antibodies antagonizing the CGRP pathway represents a novel approach to prevention: the very anticipated mechanism-specific migraine-targeted therapy. Four monoclonal antibodies are currently either in regulatory review or on the market for migraine prevention: three against CGRP itself - galcanezumab, eptinezumab, and fremanezumab, and one against the canonical CGRP receptor – erenumab (Goadsby, 2019). Although no treatment-related serious adverse events were reported, and adverse events were reported in a similar proportion of patients in the placebo and treatment groups (Tso and Goadsby, 2017; Zhu et al., 2018), the long-term safety is entirely unknown at this time, especially in terms of appetite, body weight or glucose metabolism.

3.2. Pituitary adenylate cyclase activating polypeptide

The pituitary adenylate cyclase activating polypeptide (PACAP) is a peptide first isolated from ovine hypothalamus and so named because it

stimulates the accumulation of intracellular and extracellular cAMP in monolayer cultures of rat anterior pituitary cells. It is present in two bioactive, amidated forms, a 27- or 38-amino acid neuropeptide, and shows 68% sequence homology with vasoactive intestinal peptide (VIP), belonging to the VIP/glucagon/secretin family (Gottschall et al., 1990; Miyata et al., 1989; Sherwood et al., 2000). PACAP exerts its biological action by binding to three G protein-coupled receptors subtypes, PAC_1, $VPAC_1$ and $VPAC_2$. Anatomical studies show PACAP is widespread throughout the CNS and peripheral tissue and binding sites include the TCC, spinal cord, trigeminal ganglia, sphenopalatine ganglia and CNS structures such as the thalamus, hypothalamus, and brain stem (Csati et al., 2012; Eftekhari et al., 2015; Gottschall et al., 1990; Joo et al., 2004; Masuo et al., 1992; Uddman et al., 2002b).

In migraineurs, PACAP induces migraine-like headaches when administered intravenously (Schytz et al., 2009) and systemic PACAP38 concentrations are significantly altered depending on the migraine phase (Tuka et al., 2013; Zagami et al., 2014). In animal studies, PACAP38 administered intravenously induces delayed sensitization of central trigeminovascular neurons (Akerman and Goadsby, 2015), which translates to delayed migraine-like headaches in 50% of migraine patients without aura (Schytz et al., 2009). Furthermore, PACAP has also been linked to sensitization and light aversion as mice lacking PACAP do not develop light aversion or trigeminal sensitization after nitroglycerin-induced light aversion (Markovics et al., 2012), with likely implications for migraine photophobia. More specifically, central PAC_1 receptor is considered to be an important target as intravenous administration of a PAC_1 receptor antagonist inhibited the peripheral meningeal vasodilatory effects of dural trigeminovascular nociception, whereas central (i.c.v.) administration of the PAC_1 receptor antagonist inhibited dural nociceptive trigeminovascular activation (Akerman and Goadsby, 2015). While PACAP38 infusion in the PVN increases TCC spontaneous activity (Robert et al., 2013), recent work from our laboratory has shown that, when microinjected into the VTA, PACAP38 inhibits spontaneous and noxious TCC neuronal responses (Martins-Oliveira et al., 2017b). These data indicate that there are still fundamental discoveries about the role of PACAP in nociceptive processing to be made such as examining the functional role of different PACAP receptors in specific brain areas. Meanwhile, PAC_1 receptor antibodies have been successfully used in migraine pre-clinical studies (Hoffmann et al., 2017). A phase-II study of a PAC1 antibody has been reported in abstract form to be negative, so that the VPAC receptors should be reconsidered.

Regarding a physiological role in energy balance, PACAP is involved in food intake control. Brain delivery of PACAP reduces food intake when injected i.c.v. (Morley et al., 1992; Mounien et al., 2009) or into the hypothalamic PeF (Chance et al., 1995), the PVN or the VMH (Hurley et al., 2016; Resch et al., 2011; Resch et al., 2013; Resch et al., 2014). In the hypothalamic arcuate nucleus (ARC), approximately 50% of proopiomelanocortin (POMC) neurons express both of PAC_1 and $VPAC_2$ receptors (Mounien et al., 2006) and consecutive *in vitro* studies showed that exogenous PACAP increased POMC mRNA expression, an effect further blocked by PACAP antagonist, which led scientists to suggest that PACAP regulation of feeding behavior is mediated, in part, by ARC POMC neurons. Moreover, when injected peripherally, PACAP reduces food intake through the PAC_1 receptor (Vu et al., 2015). On a related note, PACAP is also involved in endocrine regulation as PACAP is synthesized and released by pancreatic β-cells and exerts several metabolic actions, such as stimulation of insulin production and release, and increase of insulin-induced glucose uptake in adipocytes, thereby improving glucose tolerance (Nakata et al., 1999; Nakata and Yada, 2007; Yada et al., 1994).

Interestingly, recent work emphasizes the role of PACAP in hedonic feeding showing PACAP administration into specific subregions of the nucleus accumbens (NAc), part of the mesolimbic reward pathway, attenuated palatable food consumption in satiated rats, i.e., without altering homeostatic feeding (Hurley et al., 2018). A few studies highlight a putative interaction between the NAc and trigeminal pain, where CGRP elicits NAc dopamine release in a model of cephalic pain, an effect blocked by sumatriptan (De Felice et al., 2013); and stimulation of NAc inhibits nociceptive trigeminal nucleus caudalis neurons in a model of orofacial pain (Barceló et al., 2012). Furthermore, migraine patients showed altered resting-state functional connectivity between NAc and other brain structures (Yuan et al., 2013). Given that susceptible migraine patients experience food cravings it is key to determine whether this is mediated by dysfunctional PACAP activity in discrete reward pathway regions, like the NAc.

Perhaps the most important lesson from these studies is that while it is clear that PACAP plays a role in migraine pathophysiology, it is unknown whether PACAP is involved in appetite changes as well as disturbances of glucose metabolism in migraine patients. Our studies on the interaction of glucose metabolism and trigeminovascular activation (Martins-Oliveira et al., 2017a; Martins-Oliveira et al., 2017b) offer a path to investigate PACAP-mediated mechanisms and the metabolic profile of patients involved in clinical studies making use of PACAP to induce migraine-like headache.

3.3. The orexinergic system

Orexin A and B are two hypothalamic neuropeptides that bind to two G-protein coupled receptors, termed OX_1R and OX_2R, which are 64% homologous (Sakurai et al., 1998). The rat and human versions of OX_1R and OX_2R demonstrate a 94% and 95% homology, respectively, suggesting a high level of conservation across mammalian species. Orexin A has equal affinity for both OX_1R and OX_2R, while orexin B demonstrates a 10-fold higher affinity for OX_2R than OX_1R (Sakurai et al., 1998). Hypothalamic orexin neurons project throughout the CNS, including the dorsolateral pons, the VTA, the PAG, as well as to the TNC and the thalamus (Hervieu et al., 2001). These structures have each been implicated in the pathophysiology of migraine by anatomical and physiological studies (Goadsby et al., 2009) as well as by functional brain imaging (Sprenger and Goadsby, 2010). In animal studies, there is an orexinergic modulation of the trigeminovascular system (Bartsch et al., 2004a; Hoffmann et al., 2015; Holland et al., 2006). For example, intravenous orexin A and B has shown that OX_1R activation can inhibit nociceptive trigeminovascular processing in the trigeminocervical complex of the rat (Holland et al., 2006).

Furthermore, orexin A and B are closely related to the hypothalamic control of feeding and body weight. These neuropeptides were shown to stimulate food intake when injected into the brain ventricle and hypothalamic ARC (Haynes et al., 1999; Muroya et al., 2004; Sakurai et al., 1998). While orexin B has been reported to stimulate feeding, this effect is much less reliably obtained than the response to orexin-A, and this might reflect the greater importance of the OX_1R in orexin-induced hyperphagia or the more rapid *in vivo* clearance of orexin B (Smart et al., 2001). Studies have shown that metabolic challenges, such as fasting and hypoglycemia, increase orexin concentrations in the hypothalamus (Cai et al., 1999; Cai et al., 2001; Karteris et al., 2005; Sakurai et al., 1998) in a region-specific manner as levels of OX_1R mRNA were significantly increased in the VMH and the medial division of amygdala and levels of OX_2R mRNA were only increased in the ARC (Lu et al., 2000).

In addition, systemic glucose levels seem to influence orexinergic activity since orexin cells are stimulated by low glucose levels and physiological elevations of glucose levels suppress both spontaneous and evoked firing in *in vitro* electrophysiological studies (Burdakov et al., 2005). Of note, orexin-containing neurons show Fos-like immunoreactivity in insulin-induced acute hypoglycemia (Moriguchi et al., 1999) and other studies reported that fasting (Sakurai et al., 1998) and insulin-induced hypoglycemia (Cai et al., 1999; Cai et al., 2001; Griffond et al., 1999) increased prepro-orexin mRNA in the rat lateral hypothalamus (LH), whereas leptin (discussed in detail below) had the converse effect (López et al., 2000). These studies suggest that orexinergic mechanisms

might be relevant to address the mechanisms of action by which fasting/skipping meals, and therefore acute hypoglycemia, may trigger migraine – or be perceived as a trigger – in susceptible individuals.

3.4. Neuropeptide Y

Neuropeptide Y (NPY) is a peptide hormone that acts on six G-protein coupled receptor subtypes ($Y_{1\text{-}6}$) (Yulyaningsih et al., 2011) and is present in central and peripheral nervous systems, abundantly expressed in the basal ganglia, limbic system and the hypothalamus (Adrian et al., 1983).

NPY is highly synthesized in the ARC (Bai et al., 1985) and released in sites including the PVN and LH (Broberger et al., 1998; Stanley et al., 1993), making it one of the most potent appetite-stimulating peptide. The perifornical area of the hypothalamus (PeF), at the level of the caudal PVN, is the most sensitive hypothalamic site for NPY-induced eating (Stanley et al., 1993) and i.c.v. administration of NPY (Clark et al., 1984; Kalra et al., 1991) or by direct microinjection into the PVN (Stanley and Leibowitz, 1985) stimulates food intake. Given that the PVN projects directly and modulates neuronal firing in the TCC (Robert et al., 2013), it is possible that the PVN mediates appetite changes in migraine.

Furthermore, NPY secretion is regulated by peripheral signals, including the anorexigenic peptide leptin – which exerts inhibitory effect at medial hypothalamic ARC–NPY neurons (Stephens et al., 1995; Wang et al., 2008); and the orexigenic peptide orexin A – which activates NPY-containing neurons in the ARC (Yamanaka et al., 2000). It is thus possible that the hypothalamic ARC might mediate a part of migraine phenotype since ARC fibers establish putative contacts with major pain modulation brainstem regions, such as the periaqueductal gray (PAG), dorsal raphe nucleus, nucleus raphe magnus, locus coeruleus (LC), and the nucleus tractus solitaries (NTS) (Sim and Joseph, 1991). Additionally, NPY Y_1 receptor-deficient mice showed increased acute nociception (Kuphal et al., 2008) and intra-ARC administration of NPY showed that NPY and NPY Y_1 receptor activation exerts anti-nociceptive effects in intact rats and in rats with inflammation (Li et al., 2005).

In line with these results, other studies have shown an association between NPY mechanisms and migraine pathophysiology. One study reported episodic migraineurs had lower peripheral levels of NPY during fasting, compared with healthy controls, and these levels increased with amitriptyline and flunarizine preventive treatment (Caproni et al., 2011), whereas another study found fasting NPY levels were higher in migraine patients than controls (Siva et al., 2017). These differences on baseline NPY levels might be due to different vein blood collection or period of attack free days. Additionally, a study examining over 1180 genes reported NPY expression is downregulated by CSD (Choudhuri et al., 2002), the neurophysiological correlate of the migraine aura in humans (Moskowitz et al., 1993). Because NPY Y_1, Y_2 and Y_5 receptors are present in the trigeminovascular system (Parker and Herzog, 1999; Uddman et al., 2002a), one would expect NPY to have a fundamental role modulating trigeminovascular pathways. In preclinical models, NPY is known to inhibit neurogenic dural vasodilation (Williamson, 2000) or plasma protein extravasation (Yu and Moskowitz, 1996) via NPY Y_1 and NPY Y_2 receptors, respectively. Moreover, we have shown NPY inhibited trigeminovascular neuronal firing in a dose-dependent manner and this effect was mediated by the NPY Y_1 receptor (Martins-Oliveira et al., 2016). These studies might reckon a protective mechanism by NPY: since NPY is antinociceptive in pain and migraine animal models, there might be an increased demand for NPY in patients with frequent headache attacks, e.g. chronic migraine.

Importantly, fasting or food deprivation, reported by some patients to be a migraine trigger, is known to interfere with NPY pathways. While hypothalamic ARC NPY mRNA expression is up-regulated by fasting (White and Kershaw, 1990), food deprivation markedly increased NPY release in the PVN both *in vivo* (Kalra et al., 1991) and *in vitro* (Dube et al., 1992). In addition, fasting and food restriction augmented NPY Y_1 receptor mRNA in the hypothalamus (Xu et al., 1998). Because AgRP neurons expressing NPY in the ARC are reciprocally innervated by orexin LH neurons (Broberger et al., 1998; Elias et al., 1998), it is possible that hypothalamic activation seen in imaging studies during migraine could interfere with orexinergic as well as ARC NPY neuronal activity. Of note, orexins and NPY functionally co-operate resulting in an enhanced feeding behavior (Muroya et al., 2004). Given the potential interactions of orexinergic hypothalamic neurons, NPY system and the trigeminovascular system, understanding the anatomical pharmacology of these potential modulatory systems is essential to perceive feeding mechanisms in migraine.

3.5. Insulin

Insulin is a hormone secreted by the beta (β) cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism (Wilcox, 2005). Of note, insulin activity is disrupted by CGRP *in vivo* and *in vitro* (Choi et al., 1991; Leighton and Cooper, 1988; Liu et al., 2017; Molina et al., 1990; Pettersson et al., 1986) and insulin resistance is believed to be involved in the pathogenesis of obesity (Goossens, 2008; Samuel and Shulman, 2012). Interestingly, clinical studies report higher insulin levels in migraine patients, comparing to controls (Cavestro et al., 2007; Rainero et al., 2005). Moreover, a significant association between a polymorphism of 5 single nucleotides of the gene encoding for insulin receptors has been demonstrated in migraineurs (McCarthy et al., 2001) suggesting migraine might be more likely in susceptible persons when there is low insulin receptor activation (McCarthy et al., 2001). These findings may highlight a less understood interaction between insulin, CGRP and obesity. Given that a significant prevalence of insulin resistance was observed in chronic migraine patients (Fava et al., 2013; Siva et al., 2017), and obesity is associated with migraine progression from an episodic into a chronic form (Bigal and Lipton, 2006; Bigal and Lipton, 2008; Bigal and Rapoport, 2012), insulin dysfunction might be the common factor for disturbed metabolism in migraine through CGRP mechanisms.

One way of mimicking the metabolic effects of fasting is to induce hypoglycemia *via* insulin, resulting in significant activation of the PVN and extra-hypothalamic areas such as the LC, dorsal motor nucleus of the vagus, and NTS (Morilak et al., 1987; Yuan and Yang, 2002). These data are relevant because some of these areas send neuronal projections to the TCC and we have recently shown that insulin administration directly modulates TCC neuronal firing (Martins-Oliveira et al., 2017a). In addition, insulin-induced hypoglycemia activates orexinergic neurons (Tkacs et al., 2007), which are likely to be involved in migraine pathophysiology (Hoffmann et al., 2015; Holland et al., 2006).

Another factor closely related to migraine is sleep deprivation. The regulation of sleep, particularly within the hypothalamus, is strongly linked to the regulation of feeding processes, and the interaction of both of these homeostatic mechanisms is likely involved in migraine pathophysiology. Both sleep and feeding rhythms are synchronized to the environmental 24-h cycle mainly by light–dark information perceived by the eyes, and regulated within the hypothalamus. Generation of these rhythms occurs in the master circadian clock, the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Davidson et al., 2008; Yamazaki et al., 2000). The SCN output is crucial for synchronization of many metabolic and endocrine factors, such as glucose (Cailotto et al., 2005; La Fleur et al., 1999; Ruiter et al., 2003) and leptin (Kalsbeek et al., 2001). Indeed, sleep deprivation induces an increase in glucose and insulin plasmatic levels (Reynolds et al., 2012) and lower glucose tolerance in humans (Spiegel et al., 1999). Additionally, sleep debt has been shown to have a harmful impact on carbohydrate metabolism and endocrine function (Spiegel et al., 1999). Thus, it is not surprising that impaired insulin signaling pathways may have an effect on migraine

pathophysiology through sleep neurobiology disruption along with disturbed homeostatic glucose metabolism.

3.6. Glucagon

Glucagon is a polypeptide secreted from pancreatic alpha (α) cells (Lok et al., 1994) during meals and is involved in the production of postprandial satiety (Geary and Smith, 1982; Geary, 1990). In addition, peripheral glucagon activates hepatic glucagon receptors to increase hepatic glucose production (HGP), an effect that is transient (Mighiu et al., 2013). Systemic glucagon crosses the blood–brain barrier (Lorén et al., 1979) and acts within the hypothalamus. In the LH, glucagon inhibits glucose-sensitive neuronal activity, thus contributing to the control of metabolism and meal termination (Inokuchi et al., 1986). Glucagon receptor immunoreactivity is also detected in hypothalamic ARC, colocalized with AgRP neurons (Hoosein and Gurd, 1984; Mighiu et al., 2013).

Systemic glucose levels influence satiety and while hypoglycemia accelerates gastric emptying, glucagon has shown to induce delayed gastric emptying in animals and humans (Jonderko et al., 1989; Kawamoto et al., 1985; Xu and Chen, 2007). Moreover, even blood glucose changes within the normal postprandial range have a significant impact on gastric emptying in both normal subjects and patients with insulin-dependent diabetes mellitus (Schvarcz et al., 1997). This is relevant because gastric stasis is one of the premonitory symptoms reported by migraine patients (Aurora et al., 2007; Aurora et al., 2006; Parkman, 2013) and might be involved in trigeminovascular nociceptive mechanisms. Interestingly, antidopaminergic gastrointestinal prokinetic/ antiemetic drugs that accelerate or “normalize” gastric emptying, such as domperidone and metoclopramide, have been co-administered with either triptans, paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) as an effective abortive medication in the treatment of migraines and cluster headaches, as they may speed up absorption of these antimigraine agents (De Ponti, 2000). Our efforts directed towards understanding the mechanism by which glucose changes influence trigeminovascular neurons (Martins-Oliveira et al., 2017a) strengthen evidence favoring a role for glucagon in mediating migraine delayed gastric emptying. These observations raise many questions namely whether migraine patients skip meals due to delayed gastric emptying and perceived loss of appetite, which will be examined in detail below (6. Fasting/Skipping meals in migraine: voluntary or loss of appetite?).

3.7. Leptin

Leptin is a peptide secreted by the adipose tissue and circulating leptin is thought to be an indicator to the CNS of total body energy stores (Frederich et al., 1995). Leptin is transported to the brain where it crosses the blood–brain barrier (Friedman and Halaas, 1998; Weigle et al., 1997; Zhang et al., 1994) to act on the leptin receptor b (ObRb), the long form of the leptin receptor (Cohen et al., 2001; Elias et al., 1998; Myers et al., 2009; Scott et al., 2009; Tartaglia et al., 1995). Leptin activates ObRb receptor in areas that have also been implicated in the pathophysiology of migraine (Akerman et al., 2011; Goadsby et al., 2017), such as the brainstem, midbrain, hypothalamus, thalamus and cortex (Myers et al., 2009; Scott et al., 2009; Tartaglia et al., 1995). Furthermore, ObRb receptor mRNA is present in neuronal cell bodies of trigeminal motor nuclei (Grill et al., 2002).

Leptin is the main anorexigenic peptide of feeding circuits. When injected either intravenously or i.c.v., leptin activates neurons in the PVN, ARC, VMH and DMH (Elias et al., 1998; Elmquist et al., 1997; Elmquist et al., 1998; Van Dijk et al., 1996), and suppresses feeding (Shiraishi et al., 2000). During fasting, serum levels of leptin decrease, normalizing after refeeding (Kolaczynski et al., 1996; Monteleone et al., 2000). In the ARC, leptin targets POMC and AgRP/NPY neurons with opposing signaling effects: leptin activates the food suppressing POMC pathway (Schwartz et al., 1997), and actively inhibits the orexigenic AgRP/NPY pathway (Baskin et al., 1999b; Schwartz et al., 1996), and during fasting this effect is reversed.

In order to modulate trigeminal nociceptive pathways, the endocrine system sends information to the central nervous system, suggesting that eventual perturbations of homeostatic feedback mechanisms can influence the activity of the trigeminovascular system. Indeed, there is evidence of perturbations in leptin levels in migraineurs, with increased leptin and insulin levels in one study (Bernecker et al., 2010), but lower serum levels interictally in another (Guldiken et al., 2008). Furthermore, clinical studies report that the risk of chronic migraine is higher in obese migraineurs experiencing episodic migraines (Bigal et al., 2006; Bigal and Lipton, 2006), with attack frequency and severity increasing with body mass index (Bigal et al., 2006), and that morbidly obese women show a higher incidence of migraine with aura (Horev et al., 2005). Likewise, a higher migraine prevalence in metabolic syndrome patients was demonstrated comparing to the general population (Guldiken et al., 2009). Given that the development of obesity is associated with leptin resistance (Caro et al., 1996; de Git et al., 2018) it seems plausible that a neuroendocrine pathway through leptin mechanisms might mediate a potential link between these metabolic conditions and migraine. In particular, migraine animal models have shown that obesity causes abnormal sensory processing within the trigeminovascular system (Rossi et al., 2013; Rossi et al., 2016) and diet-induced obesity results in trigeminal sensitization through CGRP mechanisms (Marics et al., 2016; Marics et al., 2017). We have recently shown that leptin exerts an antinociceptive action within the TCC (Martins-Oliveira et al., 2017a) and because obesity is characterized by reduced leptin sensitivity these data could shed light on possible mechanisms mediating the association of obesity with an increased frequency and intensity of migraine (Bigal et al., 2006; Bigal and Lipton, 2006; Bigal et al., 2007). Finally, the relative secretion of leptin and insulin correlates with body fat distribution: insulin directly correlates with visceral fat, whereas leptin correlates better with subcutaneous fat (Woods et al., 2003). Therefore, in order to dissect potential disturbances of leptin and insulin secretion in migraineurs comparing to controls, future studies should examine fat distribution in migraine patients (Gelaye et al., 2017), besides of using body mass index (BMI) as a method to diagnose overweight and obesity.

Furthermore, leptin and orexins have common pathways within the hypothalamus, which highlight the potential synergistic leptin and orexinergic mechanisms in migraine pathophysiology. For example, LH ObRb neurons densely innervate and directly synapse with LH orexin neurons, and intra-LHA leptin treatment in $Lep^{ob/ob}$ animals increased the expression of LH orexin mRNA expression (Louis et al., 2010). Evidence shows that plasma orexin A levels correlate negatively and plasma leptin levels correlate positively with body mass index (BMI) (Adam et al., 2002), therefore, obese individuals should present lower plasmatic orexin A levels and higher plasmatic leptin levels when compared to normal BMI individuals. This is in accordance with the lower peripheral orexin A levels seen in episodic migraineurs (Caproni et al., 2011) and, also, with higher blood leptin levels shown in non-obese female migraineurs (Bernecker et al., 2010), comparing with healthy controls.

Work from our laboratory, making use of a model of acute nociceptive activation, where leptin levels were alleged to be physiologically normal, revealed that systemic leptin inhibits firing of dural-evoked trigeminovascular nociceptive neurons, and decreases the expression of the cell activation marker pERK in the TCC and hypothalamic ARC (Martins-Oliveira et al., 2017a). It should be noted, however, that leptin can exert different nociceptive effects depending on different models of pain, type of induced pain (acute vs chronic), site of administration of leptin and different basal levels of leptin expression (Hu et al., 2014; Kutlu et al., 2003; Li et al., 2013; Lim et al., 2009; Maeda et al., 2009; Wang et al., 2009; Watson et al., 2014), which should be considered for future experiments.

4. Understanding the orexigenic - anorexigenic circuit loop in trigeminovascular nociception

NPY is a potent hypothalamic orexigenic peptide and evidence for the physiological role for NPY in energy homeostasis derives from studies showing the regulation of NPY gene expression in the hypothalamic ARC by several peptides, and its release in the PVN (Kalra et al., 1991). Conversely, insulin and leptin are considered adiposity signals, circulating at levels proportionate to body fat mass, and participate in the inhibitory regulation of both food intake and ARC NPY gene expression through a negative feedback signaling within the hypothalamus (Baskin et al., 1999a; Schwartz et al., 1992). It should be highlighted, however, that in contrast to ARC NPY, DMH NPY signaling also affects food intake but is not under the control of leptin (Bi et al., 2003). On the other hand, glucagon is not considered an adiposity signal, but is known to decrease food intake (Woods et al., 2006).

It has been shown that insulin, leptin and glucagon inhibit TCC nociceptive activation in healthy animals (Martins-Oliveira et al., 2017a) and because NPY has the opposite effect in food intake, one would expect NPY to have a pro-nociceptive action in the same animal model. Contrary to expectations, we have shown NPY reduced trigeminovascular nociceptive activation through Y_1 receptor (Martins-Oliveira et al., 2016). This could be explained by the fact that, despite the fact of opposing roles in food intake control, there is a tight regulation of these peptides with bidirectional feedback loops to ensure that these peptides can respond rapidly and for prolonged durations in various food-accessible conditions. For instance, when NPY is infused chronically into the brain of *ad libitum*-fed rats there is an increase in leptin expression in adipose tissue, in part, via NPY-induced hyperinsulinaemia (Sainsbury et al., 1996). Because NPY administration induces a negative feedback signaling from the adipose tissue and pancreas (Sainsbury et al., 1996), NPY can exert an indirect antinociceptive action via leptin and insulin action in the TCC (Martins-Oliveira et al., 2017a). Moreover, acute i.c.v. NPY induces secretion of glucagon following fasting in *in vivo* animal experiments (Wilding et al., 1995). Thus, it is likely that overlapping intracellular signaling pathways mediate the general response to these diverse metabolic signals. An integrated view of appetite-related peptides feedback loop is described in Fig. 2.

On a different note, sleep disruptions have been implicated in metabolic dysregulation (Tsuneki et al., 2016), which may have physiological significance in migraine given that disturbance of sleep habits is a commonly listed trigger (Fukui et al., 2008; Holland, 2014; Kim et al., 2017). For instance, sleep deprivation induces an increase in glucose and insulin plasmatic levels (Reynolds et al., 2012) and lower glucose tolerance (Spiegel et al., 1999; Spiegel et al., 2005), as well as reduced leptin levels (Chaput et al., 2007; Spiegel et al., 2004a; Spiegel et al., 2004b). A recent study in rodents has confirmed that even a short period (4 h) of sleep deprivation impairs glucose tolerance by attenuating the first-phase insulin response to a glucose load (Jha et al., 2016). Knowing that migraine patients respond differently to changes of the sleep/wake cycle (van Oosterhout et al., 2018), these data point to the possibility that the combination of fasting/ skipping meals with another perceived migraine trigger, such as sleep disturbances, is likely to disrupt the signaling pathways of any of the aforementioned peptides. An important point is that parallel anabolic and catabolic pathways are both tonically active and both influenced by adiposity signals. Overall, it seems plausible that NPY might have a protective physiological role after fasting/ skipping meals, when its hypothalamic expression is increased, but this action could be compromised in migraineurs due to dysfunctional signaling or lower sensitivity to NPY, leptin, insulin or glucagon.

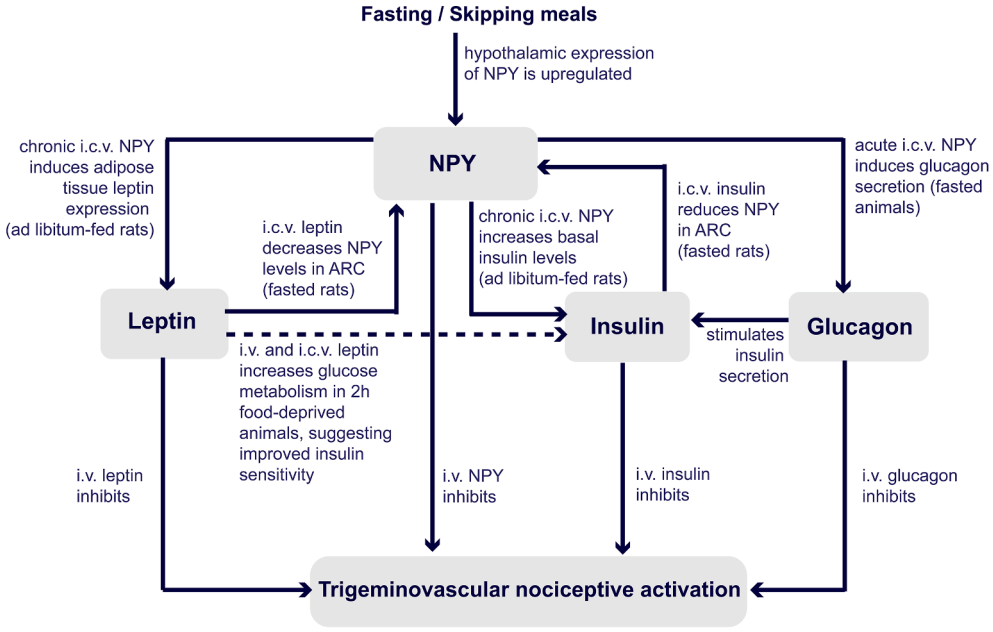

Fig. 2. Feedback mechanisms of neuroendocrine appetite control and its inputs to modulate trigeminovascular antinociception. During fasting or food deprivation, NPY expression is upregulated in the hypothalamic ARC (White and Kershaw, 1990; Xu et al., 1998). Activity of NPY is able to influence other peripheral peptides in order to maintain body-brain homeostasis. For example, when NPY is infused chronically into the brain of *ad libitum*-fed rats there is an increase in leptin expression in adipose tissue (Sainsbury et al., 1996) and basal insulin levels (Zarjevski et al., 1993). Acute i.c.v. NPY induces secretion of glucagon in fasted animals (Wilding et al., 1995). Conversely, NPY brain infusion can induce a negative feedback signaling from the adipose tissue and pancreas (Sainsbury et al., 1996). While central NPY influences peripheral insulin release pancreatic β-cells indirectly via parasympathetic pathways (Wisialowski et al., 2000), acute brain administration of insulin inhibited the fasting-related increase in ARC preproNPY mRNA levels (Schwartz et al., 1992; Sipols et al., 1995). Moreover, infusion of leptin in the brain inhibits the expression of NPY mRNA in the ARC in fasted animals (Schwartz et al., 1996). There is also a functional crosstalk between the pancreas and the adipose tissue and within the pancreas itself. Systemic injection of glucagon stimulates insulin secretion in anaesthetized mice and isolated pancreas islets through a paracrine mechanism (Song et al., 2017) and acute administration of leptin improves glucose metabolism independent of elevations in insulin levels, suggesting an improvement of insulin sensitivity (Kamohara et al., 1997). In a migraine animal model, systemic administration of NPY, leptin, insulin and glucagon is able to inhibit *in vivo* trigeminovascular nociceptive firing, impacting hypothalamic and TCC cell activation as well as blood glucose levels (Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a). These peptides have opposing roles in food intake, yet there is a tight regulation within body-brain feedback loops to maintain body homeostasis. We believe that disruption of the signaling pathways of any of these peptides is likely to disturb trigeminovascular signaling and contribute to altered feeding behavior in migraine. NPY, neuropeptide Y; i.v., intravenous; i.c.v., intracerebroventricular.

5. Glucose metabolism disturbances in migraine: the role of appetite-regulating peptides

Increasing evidence shows that glucose metabolism is disturbed in migraine, as significant prevalence of insulin resistance has been observed in chronic migraine patients (Fava et al., 2013; Siva et al., 2017). Moreover, headache is associated with high fasting glucose blood levels and migraine is specifically associated with higher insulin levels, after fasting and after the oral glucose tolerance test (Bernecker et al., 2010; Cavestro et al., 2007; Rainero et al., 2005). Glucose metabolism has been studied in a migraine animal model showing that a potential neurobiological link between migraine and impaired metabolic homeostasis may occur through disturbed glucose regulation or, on the contrary, that abnormal activation of the trigeminovascular system can deregulate blood glucose levels (Martins-Oliveira et al., 2017a). While hyperinsulinemia is an adaptive mechanism that enables the maintenance of normoglycemia in the presence of insulin resistance (Wilcox, 2005), the exact mechanisms responsible for these metabolic disturbances in the migrainous brain are yet to be fully understood.

A study using the patients as their own controls (during an attack and in the attack-free period) reported an impaired tolerance to glucose as well as lower insulin levels during the migraine attack (Shaw et al., 1977). This is in accordance with a report showing that insulin-deficiency is required for glucose intolerance (higher glycemic response) in response to hyperglucagonemia, comparing to normal controls (Sherwin et al., 1976). These data point to a primary role of insulin in impaired glucagon signaling, *via* dysfunctional or failure of negative feedback in glucose control. On the other side, it is known that glucagon is secreted during a meal, signaling the hypothalamus to reduce glucose levels. Because glucagon demonstrated antinociceptive effects in a migraine animal model (Martins-Oliveira et al., 2017a), this might explain why refeeding following food deprivation, with consequent glucagon release, can be protective and abort or improve headache in susceptible individuals.

Following food intake, plasmatic glucose and insulin levels rise and combine to suppress glucagon secretion by the pancreatic α-cell (Gerich et al., 1976; Le Marchand and Piston, 2010) and this resultant drop in plasmatic glucagon levels contributes to the reduction in hepatic glucose production and to maintenance of normal glucose homeostasis. Migraine patients showed diminished sensitivity to the hyperglycaemic action of glucagon (De Silva et al., 1974) and this can be explained by chronically elevated glucose and insulin concentrations which lead to a reduction in basal hepatic glucose production. It is also possible that chronic fasting hyperglycemia and insulin oversecretion will interfere with normal insulin/glucagon ratio and physiological nociceptive modulation.

Moreover, accurate sensing of insulin by hypothalamic insulin receptors is essential for an effective control of food intake, as well as normal control of hepatic glucose output. Convergent signals from insulin and leptin act in the CNS to regulate both nociception and glucose homeostasis (Martins-Oliveira et al., 2017a) and a defect in either peptide signaling can result in appetite changes and/or insulin resistance. It is noteworthy that acute administration of leptin in mice improves glucose metabolism (glucose output and glucose uptake), independent of elevations in plasma insulin, improving insulin sensitivity (Kamohara et al., 1997) (Fig. 2). However, clinical reports proposing insulin resistance is present in migraine do not distinguish between peripheral or central insulin resistance. Nevertheless, since reduced leptin signaling can result in systemic and central insulin resistance (Ikeda et al., 1986; Zhang et al., 1994), this suggests that leptin signaling might be impaired in migraine patients. Conversely, clinical studies evaluating leptin levels in migraineurs have been inconclusive so far and have shown contradictory results (Guldiken et al., 2008; Pisanu et al., 2016; Rubino et al., 2016). This is likely due to substantial study design differences and conflicting results limiting definitive conclusions as reported in a recent systematic review (Peterlin et al., 2016).

While the orexigenic functions of NPY signaling in CNS have been studied extensively in numerous species— both mammalian and non-mammalian, its energy regulation actions in the periphery are far less understood. Indeed, no effects have been described after peripheral infusion (Beck, 2006). Nonetheless, it is known that there is a close regulatory loop by which NPY and insulin control expression and function of each other. On one hand, central NPY influences peripheral insulin release pancreatic β-cells indirectly via parasympathetic pathways, followed by insulin action on hypothalamic NPY neurons to reduce NPY levels (Wisialowski et al., 2000). Additionally, chronic central NPY is known to cause increased basal levels of insulin (Zarjevski et al., 1993). On the other hand, acute elevation of insulin levels by direct administration into the brain was able to reduce ARC NPY levels (Schwartz et al., 1992; Sipols et al., 1995) (Fig. 2). The inhibitory tone by peripheral insulin is confirmed in a study using a diabetic rodent model of insulin deficiency and associated hyperglycemia, such as the streptozotocin rat, where NPY expression levels in the hypothalamus are strongly up-regulated (Gelling et al., 2006). In particular, the absence of insulin receptors signaling in NPY neurons also leads to a significant up-regulation of hypothalamic NPY expression (Loh et al., 2017). This suggests the development of resistance to the feedback effects of insulin on hypothalamic NPY in obesity and insulin resistant states, which are characterized by chronically elevated insulin levels (Könner and Brüning, 2012). Recently, our group has shown that exogenous administration of NPY inhibits nociceptive trigeminal inputs in a healthy animal (Martins-Oliveira et al., 2016), however what is less known is the effect of NPY associated with deficient insulin signaling, as suggested in migraineurs, which challenges further studies in migraine animal models.

It is important to address that acute changes of systemic glucose levels can alter TCC nociceptive responses, perhaps not directly, but by perturbation of the normal physiology and peptide secretion, i.e., perturbation of insulin, leptin and glucagon pathways – which consequently regulates blood glucose levels. For instance, a study by Rajendran et al. (Rajendran et al., 2001), showed that the pain threshold was modulated by insulin rather than blood glucose levels. This study demonstrated that high serum insulin levels exerted significant antinociceptive effects, irrespective of hypo-, eu- and hyperglycemia conditions. In addition, a rather small clinical study showed higher sucrose-induced serum insulin level in migraineurs comparing to controls, without development of sucrose-induced hypoglycemia (Kokavec and Crebbin, 2010). Thus, it is likely that insulin plays a predominant role through an overall direct action on nociception and indirect action on leptin and glucagon effects, through positive and negative feedback loops, respectively.

Common forms of migraine are likely to be the result of several genetic factors which interact with each other and with environmental influences that finally lead to an increase in the susceptibility of migraine (Goadsby et al., 2017). Genetic studies also suggest that migraine patients may have an increased vulnerability to altered metabolism(Gross et al., 2019b), especially glucose metabolism. Non-mitochondrial genetic evidence shows associations of migraine with polymorphisms in insulin receptor-related genes (McCarthy et al., 2001; Rainero et al., 2005) and the SLC2A1 gene which encodes the glucose transporter 1 (GLUT1) protein(Mohammad et al., 2014). The GLUT1 deficiency syndrome, a condition of impaired brain glucose transport, has been linked to hemiplegic migraine and migraine with aura (Mohammad et al., 2014). Furthermore, mitochondrial genetic evidence, including genes that encode nuclear-encoded mitochondrial proteins, suggest a generalized metabolic dysfunction in migraine, where suboptimal mitochondrial functioning together with an imbalance between energy supply and demand may increase migraine susceptibility (Gross et al., 2019b). Given that mitochondria, vital organelles that provide cellular energy, play a pivotal role in insulin signaling(Cheng et al., 2010), it is likely that the suboptimal

mitochondrial functioning may lead to the impaired insulin sensitivity observed in migraine patients (Cavestro et al., 2007; Rainero et al., 2005).

6. Fasting and/or skipping meals in migraine: voluntary or loss of appetite?

Brain systems interact to maintain energy homeostasis and the bidirectional interaction of feeding and sensory processing of pain has been specifically examined in a migraine animal model, where Malick and Burstein (2001) found that noxious stimulation of the dura mater in conscious rats induced a transient suppression of food intake, through activation of neuronal populations in the medullary dorsal horn areas, in parabrachial and hypothalamic neurons. Conversely, motor withdrawal responses to an acute painful stimulus are inhibited during feeding behavior, through the action of brainstem pain-modulatory neurons (Foo and Mason, 2005; Mason and Foo, 2009). More recent work, making use of genetically encoded optogenetic and pharmacogenetic tools showed that food deprivation-induced hunger selectively blocks inflammatory phase pain responses but has no effect during the acute phase response to chemical, thermal or mechanical pain (Alhadeff et al., 2018).

At this point, it is useful to highlight the notion that fasting is a conscious decision to skip meals, a voluntary action; whereas skipping meals refers to depriving oneself of food and it may occur without intention. Most of the literature in headache research use both terms interchangeably and regardless of the metabolic differences, we use fasting and/or skipping meals unless the original research study clearly states one or another.

Skipping meals is one of the most consistent triggers reported by migraine patients and these studies bring our attention to the important fact that it is still unclear whether skipping meals is a cause or a consequence of abnormal nociceptive TCC activation in migraine.

As a cause, food deprivation through voluntary abstention from food is exemplified by religious fasting, e.g. “Yom Kippur Headache” and “First of Ramadan Headache”. Clinically, the fasting headache is more likely to develop in patients with a history of headache and increases with the duration of the fast (Mosek and Korczyn, 1995), and intermittent fast and fluid restriction increases the frequency of migraine attacks (Abu-Salameh et al., 2010). Evidence indicates that there is a small weight and fat mass loss during the month-long Ramadan, regained 4 weeks afterwards (Fahrial Syam et al., 2016; Hajek et al., 2012; Norouzy et al., 2013) and a reduction on fasting blood glucose levels (Ibrahim et al., 2008; Kul et al., 2014). In healthy females, serum leptin levels progressively increase and NPY levels decrease throughout the month (Kassab et al., 2004; Kassab et al., 2003). Although the underlying mechanism responsible for headache during religious fasting is unclear, there is evidence that shifting meal timing causes a comparable shift in plasma hormonal rhythm (Johnston, 2014). Perhaps this shift in circadian rhythm, in patients with headache history, has a central role in modulation of pain. It would be interesting to examine the variation of metabolic parameters (e.g. leptin, insulin and NPY) during religious fasting in headache patients.

Note that voluntary abstention from food can indeed delay a meal, yet it is the unnoticed way of skipping meals caused by involuntary loss of appetite that we would like to bring attention to herein. Indeed, gastric motility may play a role in loss of appetite leading the unaware migraine patient to skip meals. Glucagon can induce increased postprandial satiety and delayed gastric emptying (Jonderko et al., 1989), which may have appetite-suppressing effects (Goyal et al., 2019). Of note, increased fasting glucagon levels and delayed glucagon suppression, together with increased circulating insulin levels, develop in parallel with insulin resistance (Færch et al., 2016). Given that insulin sensitivity is impaired in migraineurs (Bernecker et al., 2010; Cavestro et al., 2007; Fava et al., 2013; Rainero et al., 2005; Siva et al., 2017) and glucagon is able to inhibit TCC nociceptive activation in healthy animals (Martins-Oliveira et al., 2017a), it is possible that glucagon signaling is disrupted through insulin mechanisms. One study comparing fasting hepatic gluconeogenesis by administering glucagon in migraineurs and control subjects (De Silva et al., 1974) has shown that the maximal rise in blood glucose levels was lower in migraine patients, suggesting the normal hyperglycemic response might be impaired in these patients. These clinical studies and others (Martins-Oliveira et al., 2017a) suggest that glucagon signaling pathway might be impaired at the level of gluconeogenesis in the liver, as well as within the TCC, which can eventually cause glucagon oversecretion as part of a feedback mechanism. Consistent with this view, abnormal glucagon signaling together with impaired insulin sensitivity would increase systemic glucose levels, thereby inducing delayed gastric emptying. This viewpoint is supported by the fact that migraine attacks have been linked to gastric stasis, with studies reporting slower gastric emptying during the attack as well as interictally (Aurora et al., 2007; Aurora et al., 2006; Aurora et al., 2013). Remarkably, abortion of the migraine attack is facilitated when acute migraine medication is administered together with gastroprokinetic medication (Volans, 1975; Volans, 1978). Fig. 3 describes a hypothetical explanation of environmental and sensory factors leading to fasting or skipping meals in migraine.

Overall, the data suggests migraine attacks emerge due to a disorder of brain sensory processing that itself likely cycles, influenced by genetics and the environment. Following CNS (central nervous system) disruption and activation of structures involved in homeostasis (e.g. hypothalamus, etc.), altered neuroendocrine signaling occurs leading to changes in satiety and metabolism (e.g. glucose metabolism). These will most likely impact feeding behavior - already part of the symptomatology of the ongoing attack yet creating the illusion of a trigger and misinterpreted by the patient. Whether metabolic and satiety imbalances during the migraine episode are (undesirable) consequences of the migraine pathophysiology itself or rather contribute to restore brain energy homeostasis - as a protective, adaptive and temporary response to meet the cerebral energy needs - remains unknown (Goadsby et al., 2017; Gross et al., 2019b; Martins-Oliveira et al., 2017a).

A feature of the glucose metabolism includes the production of ketone bodies through dietary ketosis which has been studied in several neurological diseases and has been associated with headache symptoms improvements (Augustin et al., 2018; Murano et al., 2021). Ketone bodies mediate several biological mechanisms namely glucose transport, mitochondrial function, oxidative stress, neural excitability, neuroinflammation and the gut microbiota (Murano et al., 2021). Ketogenic diets act through a combination of mechanisms, which are linked to the effects of ketones and dietary glucose restriction, and to interactions with receptors, channels, and metabolic enzymes (Augustin et al., 2018). Although the specific mechanisms of ketogenic diet therapy in migraine prevention are still uncertain, as well as other dietary approaches lacking evidence (Eigenbrodt et al., 2021), it has been proposed that dietary ketosis restores brain metabolism and excitability (Gross et al., 2019b). This is supported by the positive outcome in a small, controlled trial of a ketogenic diet (Di Lorenzo et al., 2019). In preclinical models, the susceptibility to cortical spreading depression (CSD) - the animal correlate of the human aura - is strongly modulated by metabolism, namely hypoxia and cerebral glucose availability, and treatment with a middle chain triglyceride enriched ketogenic diet, as an alternative energy substrate to glucose, showed protective effects against CSD (reviewed in detail elsewhere (Gross et al., 2019a)). Moreover, dietary ketosis is effective in enhancing the sensitivity of the insulin receptor and improving glycemic control (Augustin et al., 2018). Given that dietary ketosis involves reduced carbohydrate ingestion, possible mechanisms for the metabolic health benefits in migraine patients may include glycemic stabilization (lower blood glucose levels and glycemic fluctuations) and improved systemic insulin sensitivity (reduced insulin secretion and thus reduced fluctuation of insulin levels). Taking into consideration the extensive metabolic effects of dietary ketosis and its metabolic parallelism with fasting, it is possible that

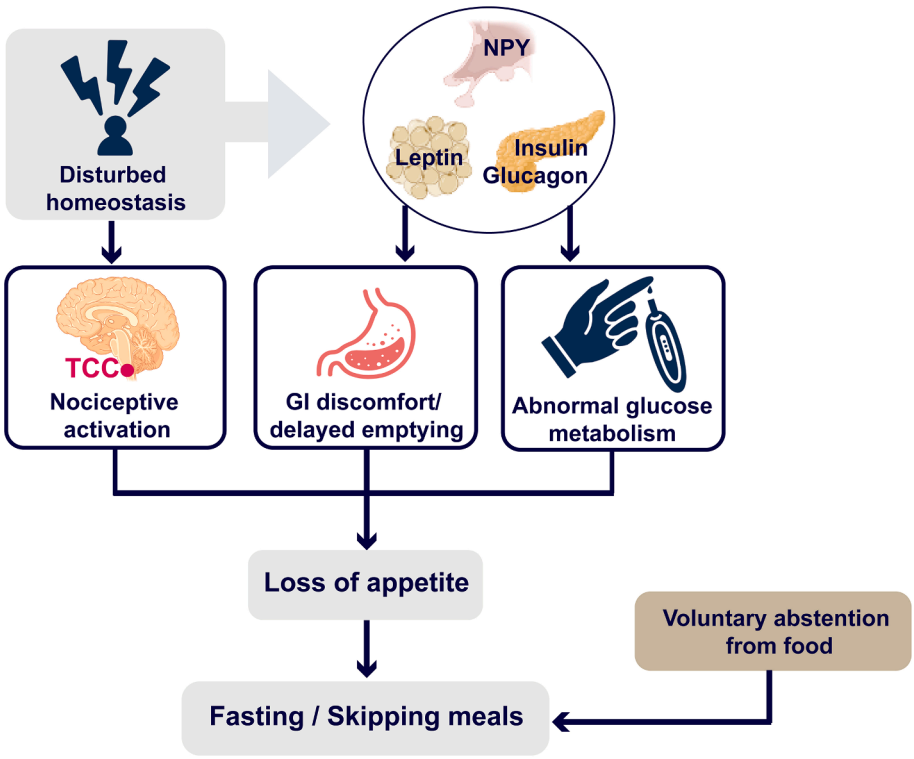

Fig. 3. Potential mechanisms involved in fasting/ skipping meals in migraine. Fasting/ skipping meals can be mediated by either loss of appetite or voluntary abstention from food. The latter is known to cause headache e.g., "Yom Kippur Headache" (Abu-Salameh et al., 2010; Mosek and Korczyn, 1995). Importantly, loss of appetite can occur as a consequence of abnormal nociceptive TCC activation, gastroparesis or disrupted glucose metabolism –factors that have been described in the context of migraine in human and animal studies (Aurora et al., 2007; Aurora et al., 2006; Aurora et al., 2013; Bernecker et al., 2010; Cavestro et al., 2007; Fava et al., 2013; Malick et al., 2001; Rainero et al., 2005; Siva et al., 2017). Moreover, disturbed homeostasis, for instance induced by the self-reported perceived migraine triggers sleep disruption and "let-down stress" (Fukui et al., 2008; Goadsby et al., 2017; Holland, 2014; Kelman, 2007; Kim et al., 2017; Lipton et al., 2014; Park et al., 2016), impacts both glucose metabolism and appetite-regulating peptides, like insulin and leptin (Chaput et al., 2007; Jha et al., 2016; Reynolds et al., 2012; Spiegel et al., 1999; Spiegel et al., 2004a; Spiegel et al., 2004b; Spiegel et al., 2005; Tsuneki et al., 2016). Appetite-regulating peptides are released by the hypothalamus (NPY), adipose tissue (leptin) and pancreas (glucagon, insulin) and can alter satiety through gastric motility and blood glucose regulation. Given that gastric motility is a key mediator of hunger/satiety and gastric stasis is able to induce loss of appetite (Janssen et al., 2011), it is possible that gastroparesis observed in migraine patients leads the patient to skip meals. The fact that exogenous administration of appetite- and glucose-regulating peptides modulates trigeminovascular nociceptive activation (Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a), highlights the importance of metabolic pathways in migraine.

the loss of appetite (speculated in the pathophysiological model presented herein as a premonitory symptom indirectly through skipping meals) could be an adaptive form of compensation to restore the brain energy homeostasis. Based on available evidence, future studies including high-quality randomized controlled trial data on dietary ketosis are necessary to further specify the roles of components in ketone bodies and their putative therapeutic targets and related pathways in migraine patients. Given that human nutritional intervention studies are challenging to conduct and may impact future meta-analysis of effects, a few notes should be taken into consideration: the ketogenic diet causes ketosis and simulates the physiological state of fasting, yet not every low-carbohydrate diet is ketogenic and, thus, ketosis should be technically confirmed; the ketogenic diet comprises several sub-type diets (Kirkpatrick et al., 2019) and, hence, the detailed protocol should be fully disclosed; importantly, adherence to ketogenic diet is particularly challenging because it comprises a very limited number of allowed foods that will likely influence diet palatability and consequently the biopsychosocial profile of migraine patients. Thus, referral to a registered dietitian (RD) for medical nutrition therapy and lifestyle counseling in migraine is advisable (Kirkpatrick et al., 2019).

7. Integration of contrasting feeding behaviors: skipping meals vs food craving

The link between both feeding behaviors – skipping meals and food craving - is hard to reconcile due to the majority of the studies being retrospective and to the fact that only recently investigation of the premonitory phase of the migraine has expanded. Even though both may occur in the premonitory phase, migraine symptomatology associates with many inter-individual differences and, additionally, there are no data confirming both occur in the same individual and in the same phase. It is possible the same patient develops food cravings after skipping meals, yet a cause-and-effect relationship is difficult to clarify with the current available scientific evidence. Neuronal fluctuations and functional reorganization of the brain throughout the migraine cycle may play a role.

Given that natural fluctuations in neuronal excitability in the brain have been observed (Fox and Raichle, 2007) and sensitization is a fluctuating phenomenon, it is likely that the brain may be naturally protected at times of lower excitability, but much more sensitive at the peak of excitability fluctuations (Goadsby et al., 2017). Findings from brain imaging studies show that resting brainstem function fluctuates over the migraine cycle (Meylakh et al., 2021) along with functional reorganization of networks between subcortical structures involved in migraine pathophysiology, with distinct results throughout the migraine cycle, namely altered hypothalamic-brainstem connectivity (Karsan and Goadsby, 2018; Schulte and May, 2016). In addition, the ongoing alterations in connectivity between the pons and cortical regions continue to mediate non-painful symptoms, homeostatic dysregulation, etc. (Karsan et al., 2020a). These functional connectivity alterations suggest that there is altered subcortical-cortical network integrity in areas of the brain involved in homeostatic functions and some of these alterations continue into the headache phase. Given the central role of the hypothalamus in appetite regulation, these connectivity alterations may account for the putative appetite changes reported by patients, i.e., it is possible that fluctuations in appetite and consequently feeding behavior occur in parallel with brain connectivity fluctuations. Nonetheless, to what extent appetite fluctuates in people with migraine compared to healthy individuals is currently unknown.

8. Key messages and the way forward

In this review, we emphasized the substantial overlap between feeding behavior, energy metabolism and migraine. The fact that specific neuronal populations govern appetite and play a role in migraine pathophysiology is relevant because unlocking this overlap of neural networks will help determine locations (and its pharmacology) with which to target for migraine therapy. The data points to an improvement of the knowledge of appetite neurobiology by using migraine animal models that builds up on clinical studies. However, many fundamental questions remain unanswered, which raises new challenges for future research.

An important first step is to pursue the potential behavioral relevance of earlier cellular and *in vivo* observations (Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a), i.e. future studies must be able to use conscious migraine animal models and should explore alterations of feeding schedules, using feeding behavioral paradigms. It would be noteworthy to test the cumulative effects of food deprivation and other premonitory symptoms, such as yawning, photophobia, sleep disturbances, allodynia, stress and/or anxiety by using more complex paradigms. Likewise, using obesity animal models is a valid way to test the effect of specific appetite-related peptides as it has been demonstrated the existence of an abnormal sensory processing within the trigeminovascular system in both high fat diet and leptin deficient mouse models of obesity (Rossi et al., 2013; Rossi et al., 2016).

Another challenge is to improve characterization of food craving symptoms by improving accuracy of data collection in clinical neuroscience studies (Taylor, 2019). A better characterization of the premonitory phase of a migraine attack in terms of feeding behavior could give clues to study and define neural maps of circuits and signaling molecules, and eventually could make it possible to design drugs to tackle the migraine attack at its very earliest stages. Migraine patients report food cravings (Giffin et al., 2003b; Karsan et al., 2021; Schulte et al., 2015), yet what is less clear is whether these patients effectively ingest the craved food, whether it is in a compulsive overeating manner or whether it is after skipping a meal. Answering each of these three discrete questions will implicate different neurobiological mechanisms and thus detail-oriented questions will definitely direct research to more exciting breakthroughs.

An observation worth noting is that the reporting frequency of uncomfortable and hurting non-headache symptoms (e.g. photophobia, phonophobia, nausea, vomiting, stiff neck, difficulty concentrating and irritability) is higher than food craving in the premonitory phase (Drummond and Lance, 1984b; Giffin et al., 2003b; Schoonman et al., 2006; Schulte et al., 2015). It is assumed that retrospective studies are open to recall bias and that the most severe symptoms may be selectively recalled and other may be forgotten (Giffin et al., 2016). Interestingly, a suboptimal recognition of premonitory symptoms during spontaneous attacks, or conversely over-reporting during the triggered attack, has been highlighted by a recent study (Karsan et al., 2020b) comparing triggered attacks (data acquired prospectively) to spontaneous attacks (retrospective recall). For instance, photophobia was more commonly triggered by nitroglycerin than reported spontaneously. This may be explained by the fact that a patient would notice photophobia more in a bright hospital room where the subject has little else to concentrate on and is asked specifically about it. In line with these observations, it is possible patients will be more likely to remember and report aversive and painful symptoms rather than appetitive symptoms like pleasurable cravings for chocolate, “salty fatty” foods, sugary drinks or sex, because the perception of pain is heightened.

On the other hand, common and nonspecific nonheadache symptoms such as yawning, food craving, and fatigue are also experienced on a day-to-day basis by the general population (i.e. not suffering from migraine). For example, a recent study using glyceryl trinitrate (GTN) as a trigger (Onderwater et al., 2020) showed that craving for sweets was not significantly different between GTN responders and healthy controls, as opposed to nausea that was a specific symptom in GTN responders for an impending GTN-induced migraine-like headache, though it is debatable the occurrence of craving for sweets while the patient feels nauseous.

Food craving may not be a specific early warning signal for the onset of migraine, but we believe it is meaningful and, in our experience, when assessing a patient it is essential to inform that specific premonitory symptoms can be associated with appetitive behavior so that in following migraine attacks the patient is aware and recognizes it, leading to a better understanding of its own attack and likeliness to report it.

Furthermore, the study of hard-wired neural circuits mediating competing motivational states, such as pain, hunger, thirst, fear or social interaction, has gained momentum with several reports demonstrating prioritization of behavior (Alhadeff et al., 2018; Burnett et al., 2016; Essner et al., 2017). Interestingly, hunger/food craving persists throughout the headache pain phase (Giffin et al., 2003a) and is a frequently reported true postdrome symptom in adults and children with migraine (Giffin et al., 2003a; Giffin et al., 2016; Mamouri et al., 2018).

A disorder is a disturbance of the normal homeostasis (Goadsby et al., 2017) and it is becoming clear that mechanisms regulating appetite and thirst homeostasis, as well as hedonic hunger, are compromised in migraine (Martins-Oliveira et al., 2016; Martins-Oliveira et al., 2017a). These neuropeptides potentially involved in feeding-related premonitory symptoms may make attractive therapeutic targets and developing mechanism-based therapies could tackle the desirable need to treat migraine patients with migraine medicines, i.e. developed specifically for migraine (Goadsby, 2016). Based on studies reported herein, several neuropeptides emerge as powerful and promising key targets in the prophylactic and acute treatment of migraine (Ong et al., 2018) and potentially co-morbidities related to eating disorders and insulin sensitivity. For example, the highly anticipated humanized CGRP monoclonal antibodies are the first mechanism-specific class of migraine preventive medications. In addition, clinical efficacy of drugs targeting PACAP or its receptors is gaining momentum and a Phase II clinical trial assessing the efficacy and safety of a monoclonal antibody against the PAC_1 receptor is ongoing (NCT03238781) (Ong et al., 2018). Moreover, following disappointing studies with dual orexin receptor antagonists due to sleep-related side effects, interest still remains in single orexin receptor antagonists. Other promising key receptor targets, such as the NPY Y_1, leptin, insulin and glucagon, remain to be fully characterized in the context of migraine drug design and development. Furthermore, targeting these neuropeptides for drug development should consider potential adverse effects due to their involvement in several homeostatic control mechanisms other than feeding behavior.

So what to answer to the burning question “Was it something I ate?”? The take-home message is that certain lifestyle modifications, such as specific dietary restrictions, are not evidence-based recommendations to treat or prevent migraine due to lack of randomized clinical trials. In addition, consistent with evolving literature, skipping meals may not be interpreted as a (perceived) trigger of migraine by patients, but rather likely to be an early premonitory manifestation.

Declaration of Competing Interest

MMO (margarida.martinsoliveira@nms.unl.pt) declare no competing financial interests. IT (isatav@med.up.pt) declare no competing financial interests. PJG reports, unrelated to this report, grants and personal fees from Amgen and Eli-Lilly and Company, grant from Celgene, and personal fees from Aeon Biopharma, Allergan, Biohaven Pharmaceuticals Inc., Clexio, Electrocore LLC, eNeura, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Novartis, Pfizer, Praxis, Sanofi, Santara Therapeutics, Satsuma, and Teva Pharmaceuticals, and personal fees for advice through Gerson Lehrman Group and Guidepoint, fees for educational materials from Massachusetts Medical Society, Medery, Medlink, PrimeEd, UptoDate, WebMD, and publishing

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